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Assessing the clinical benefit of systemic anti-cancer treatments in the Netherlands: The impact of different thresholds for effectiveness

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ABSTRACT

Background: In the Netherlands, the clinical benefit of systemic anti-cancer treatments (SACTs) is assessed by the Committee for the Evaluation of Oncological Agents (cieBOM). For non-curative SACTs, the assessment is based on the hazard ratio (HR) for progression-free survival and/or overall survival (OS), and the difference in median survival. We evaluated the impact of different thresholds for effectiveness by reassessing the clinical benefit of SACTs.

Methods: We reassessed SACTs that were initially assessed by cieBOM between 2015 and 2017. Four scenarios were formulated: replacing an "*OR*" approach (initial assessment) by an "*AND*" approach (used in all scenarios), changing the HR threshold from < 0.70 (initial assessment) to < 0.60, changing the threshold for the difference in median survival from > 12 weeks (initial assessment) to > 16 weeks, and including thresholds for OS rates. The outcomes of these scenarios were compared to the outcomes of the initial assessment.

Results: Reassessments were conducted for 41 treatments. Replacing the "*OR*" approach by an "*AND*" approach substantially decreased the number of positive assessments (from 33 to 22), predominantly affecting immunotherapies. This number further decreased (to 21 and 19, respectively) in case more restrictive thresholds for the HR and difference in median survival were used. Including thresholds for OS rates slightly mitigated the impact of applying an "*AND*" approach.

Conclusions: The scenario-specific thresholds had a substantial impact; the number of negative assessments more than doubled. Since this was not limited to treatments with marginal survival benefits, understanding the potential challenges that may arise from applying more restrictive thresholds is essential.

1. Introduction

Over the past decades, the introduction of multiple new systemic anti-cancer treatments (SACTs) has led to an improvement in survival rates among cancer patients. [1,2] Although many of these treatments are considered to be of great value for patients, some offer only marginal benefits. Moreover, the high costs and healthcare resource use associated with SACTs pose a major challenge to health authorities. [3] In order to ensure affordable cancer care and appropriate use of limited healthcare resources, it is essential to assess the clinical benefit of new SACTs.

In 2015, the European Society for Medical Oncology (ESMO) introduced the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). This tool has been developed to stratify the magnitude of clinical benefit that can be expected from SACTs. Every new SACT that receives approval from the European Medicines Agency and the United States Food and Drug Administration is assigned a score, which is based on prognosis, response, survival, quality of life (QoL), and/or adverse

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events (AEs). In the non-curative setting, the highest possible scores are 4 and 5, indicating a substantial magnitude of clinical benefit. The maximal preliminary score takes into account the survival benefit and the lower limit of the 95% confidence interval (CI) for the hazard ratio (HR), and depends on the primary endpoint of the randomized controlled trial (RCT) on which the assessment is based. These scores can be downgraded and/or upgraded, depending on the primary endpoint, to reflect secondary endpoints such as QoL and AEs. SACTs that obtain a final score of 4 or 5 will be mentioned in the ESMO guidelines, with the hope that they will be reimbursed rapidly by all health authorities across the European Union. [4,5].

In the Netherlands, the clinical benefit of newly registered SACTs is assessed by the Committee for the Evaluation of Oncological Agents (cieBOM; in Dutch: Commissie ter Beoordeling van Oncologische Middelen). This committee, consisting of medical oncologists and pulmonologists, was established in 1999 by the Dutch Society for Medical Oncology (NVMO) with the aim of achieving national agreement on the use of treatments in clinical practice. Since 2009, the Dutch Society for Pulmonary Medicine and Tuberculosis has also become a part of this committee. In order to assess the clinical benefit, cieBOM developed the so-called PASKWIL criteria. [6] These criteria consist of multiple items, including effectiveness, AEs, QoL, and treatment burden.

For non-curative SACTs, the outcome of the assessment, which is either (preliminary) positive or negative, is only based on effectiveness. Whether progression-free survival (PFS) or overall survival (OS) is decisive depends on the primary endpoint(s) of the RCT on which the assessment is based. For many years, the assessment was positive if the difference in median PFS and/or OS between the new treatment and the comparator was more than 12 weeks, *OR* if the point estimate of the HR for PFS and/or OS was less than 0.70. In May 2023, cieBOM introduced a revised version of the PASKWIL criteria, with the most important revision being the replacement of the "*OR*" approach by an "*AND*" approach. Furthermore, for RCTs where the median OS in the comparator arm is less than or equal to one year, the assessment is now based solely on OS, instead of either PFS or OS. Finally, for RCTs where the median OS in the comparator arm is more than one year, the threshold for the difference in median survival (either PFS or OS) changed to more than 16 weeks. [7].

To evaluate the impact of different thresholds for effectiveness (in terms of PFS and OS), we reassessed the clinical benefit of non-curative SACTs that were initially assessed by cieBOM using the PASKWIL criteria applicable at the time of the initial assessment.

2. Methods

CieBOM's assessment reports are published on the website of the NVMO. [8] From this website, we selected all reports involving non-curative SACTs that were published between January 2015 and December 2017. We did not select reports concerning a reassessment.

Data were derived from cieBOM's assessment reports [8], phase II or III RCTs, and ESMO-MCBS Scorecards [9] using a standardized data collection form in Excel. The following data were extracted: report details (date of publication on the NVMO website, treatment, and indication), study characteristics (study design, study name, experimental arm, comparator arm, and primary endpoints), effectiveness outcomes (median PFS and OS, OS rates, and HRs for PFS and OS), and the ESMO-MCBS score.

To evaluate the impact of different thresholds for PFS and OS, four scenarios were formulated based on input from cieBOM (see Table 1). The outcomes of these scenarios were compared to the outcomes of the initial assessment. In the first scenario, we applied the previous thresholds for the difference in median survival (> 12 weeks) and the point estimate of the HR (< 0.70) but replaced the "*OR*" approach by an "*AND*" approach. This approach was also applied to all subsequent scenarios. In the second scenario, an HR threshold of less than 0.60 was used. For RCTs where the median OS in the comparator arm is more than one year, the threshold for the difference in median survival was changed to more than 16 weeks in the third scenario. This scenario aligns most closely with the revised PASKWIL criteria. Finally, in the fourth scenario, we examined the inclusion of thresholds for OS rates. An increase of at least 10% in the two-year OS rate was used for RCTs where the median OS in the comparator arm was less than or equal to one year, and an increase of at least 10% in the three-year OS rate for RCTs where the median OS in the comparator arm was more than one year. For this scenario, we formulated two sub-scenarios to assess the impact of accounting for long-term outcomes (a), as the assessments are usually based solely on original RCT publications, and for the lower limit of the 95% CI for the HR (b).

Table 1
Scenario-specific PASKWIL criteria.

	Median OS in comparator arm ≤ 1 year		**Median OS in comparator arm > 1 year**	
	PFS	**OS**	**PFS**	**OS**
Scenario 1	Difference in median PFS > 12 weeks *AND* HR < 0.70	Difference in median OS > 12 weeks *AND* HR < 0.70	Difference in median PFS > 12 weeks *AND* HR < 0.70	Difference in median OS > 12 weeks *AND* HR < 0.70
Scenario 2	Difference in median PFS > 12 weeks *AND* HR < 0.60	Difference in median OS > 12 weeks *AND* HR < 0.60	Difference in median PFS > 12 weeks *AND* HR < 0.60	Difference in median OS > 12 weeks *AND* HR < 0.60
Scenario 3	Difference in median PFS > 12 weeks *AND* HR < 0.70	Difference in median OS > 12 weeks *AND* HR < 0.70	Difference in median PFS > 16 weeks *AND* HR < 0.70	Difference in median OS > 16 weeks *AND* HR < 0.70
Scenario 4[a]	Difference in median PFS > 12 weeks *AND* HR < 0.70	Difference in median OS > 12 weeks *AND* HR < 0.70, *OR* difference 2-year OS rate ≥ 10%	Difference in median PFS > 16 weeks *AND* HR < 0.70	Difference in median OS > 16 weeks *AND* HR < 0.70, *OR* difference 3-year OS rate ≥ 10%

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a] Sub-scenarios 4a and 4b assess the impact of accounting for long-term outcomes and for the lower limit of the 95% CI for the HR, respectively.

The rationale for the outcome of the assessment is provided in Supplementary Table 1. If the median PFS and/or OS was not (yet) reached in the experimental arm, the difference in median survival was estimated based on the median survival in the comparator arm and the HR. Further, in case the assessment was based on more than one RCT and the RCTs provided conflicting outcomes, the treatment was considered not assessable.

3. Results

In total, 43 assessment reports involving non-curative SACTs were published on the website of the NVMO between 2015 and 2017. Two reports concerned a reassessment, and were therefore not selected. The report details, study characteristics, and ESMO-MCBS scores of the remaining 41 reports are presented in Table 2. Nivolumab (monotherapy or in combination with ipilimumab) and pembrolizumab were the most frequently assessed treatments (15% and 10% of all reports, respectively). Most reports involved treatments for lung cancer (27%; n = 11), melanoma (15%; n = 6), or breast cancer (10%; n = 4). Almost all reports (90%; n = 37) were based on one or more phase III RCTs: 35 reports were based on one RCT and two reports on two RCTs. PFS was the primary endpoint in 21 RCTs (49%) and OS in 16 RCTs (37%); PFS and OS were both primary endpoints in five RCTs (12%). More than half of the RCTs (53%) obtained an ESMO-MCBS score of 4 or 5.

A summary of the outcomes of the initial assessment and scenarios is

Table 2
Report details, study characteristics, and ESMO-MCBS scores.

Publication date cieBOM's assessment report	Treatment	Indication	Study name	Study design	Experimental arm (s)	Comparator arm (s)	Primary endpoint (s)	ESMO-MCBS score
12-02-2015	Ramucirumab	Advanced gastric cancer (second line)	RAINBOW [30]	Phase III RCT	Ramucirumab + paclitaxel	Paclitaxel + placebo	OS	2
19-03-2015	Cabozantinib	Advanced medullary thyroid cancer	EXAM[29]	Phase III RCT	Cabozantinib	Placebo	PFS	3
02-05-2015	Bevacizumab	Platinum-resistant ovarian cancer	AURELIA[20]	Phase III RCT	Bevacizumab + chemotherapy	Chemotherapy	PFS	4
28-05-2015	Bevacizumab	Advanced cervical cancer	GOG 240[23]	Phase III RCT	Bevacizumab + chemotherapy	Chemotherapy	OS; AEs	3
06-07-2015	Lanreotide	Metastatic enteropancreatic neuroendocrine tumors	CLARINET [31]	Phase III RCT	Lanreotide	Placebo	PFS	3
05-10-2015	Nivolumab	Advanced melanoma	CheckMate 066[32]	Phase III RCT	Nivolumab	Dacarbazine	OS	4
05-10-2015	Nivolumab	Advanced squamous cell NSCLC (second line)	CheckMate 017[33]	Phase III RCT	Nivolumab	Docetaxel	OS	5
15-02-2016	Dabrafenib + trametinib	Advanced melanoma	Combi-V[15]	Phase III RCT	Dabrafenib + trametinib	Vemurafenib	OS	5
			Combi-D[16]	Phase III RCT	Dabrafenib + trametinib	Dabrafenib + placebo	PFS	4
15-02-2016	Pembrolizumab	Advanced melanoma	KEYNOTE-006 [17]	Phase III RCT	Pembrolizumab	Ipilimumab	PFS; OS	4
15-02-2016	Vemurafenib + cobimetinib	Advanced melanoma	coBRIM[34]	Phase III RCT	Vemurafenib + cobimetinib	Vemurafenib + placebo	PFS	4
04-04-2016	Crizotinib	Advanced NSCLC	PROFILE 1014 [35]	Phase III RCT	Crizotinib	Chemotherapy	PFS	4
07-06-2016	Lenvatinib	Refractory thyroid cancer	SELECT[36]	Phase III RCT	Lenvatinib	Placebo	PFS	2
07-06-2016	Necitumumab + gemcitabine + cisplatin	Advanced squamous cell NSCLC	SQUIRE[37]	Phase III RCT	Necitumumab + gemcitabine + cisplatin	Gemcitabine + cisplatin	OS	1
07-06-2016	Nintedanib + docetaxel	Advanced NSCLC (second line)	LUME-Lung 1 [38]	Phase III RCT	Nintedanib + docetaxel	Docetaxel + placebo	PFS	NA
04-07-2016	Docetaxel + ADT	Metastatic hormone-sensitive prostate cancer	CHAARTED [18]	Phase III RCT	Docetaxel + ADT	ADT	OS	4
			STAMPEDE [19]	Phase III RCT	Docetaxel + ADT	ADT	OS	4
04-07-2016	Nivolumab	Advanced ccRCC (second or third line)	CheckMate 025[11]	Phase III RCT	Nivolumab	Everolimus	OS	5
02-10-2016	Nivolumab	Advanced non-squamous NSCLC	CheckMate 057[12]	Phase III RCT	Nivolumab	Docetaxel	OS	5
02-10-2016	Ramucirumab + FOLFIRI	Metastatic colorectal cancer (second line)	RAISE[39]	Phase III RCT	Ramucirumab + FOLFIRI	FOLFIRI + placebo	OS	1
21-11-2016	Nivolumab + ipilimumab	Advanced melanoma	CheckMate 067[40]	Phase III RCT	Nivolumab + ipilimumab	Ipilimumab	PFS; OS	4
21-11-2016	Ramucirumab + docetaxel	Advanced NSCLC (second line)	REVEL[41]	Phase III RCT	Ramucirumab + docetaxel	Docetaxel + placebo	OS	1
21-11-2016	TAS-102	Refractory metastatic colorectal cancer	RECOURSE [42]	Phase III RCT	TAS-102	Placebo	OS	3
20-12-2016	Cabozantinib	Advanced ccRCC (second line or higher)	METEOR[21]	Phase III RCT	Cabozantinib	Everolimus	PFS	3
20-12-2016	Everolimus	Advanced, non-functional neuroendocrine tumors	RADIANT-4 [43]	Phase III RCT	Everolimus	Placebo	PFS	3
13-02-2017	Eribulin	Metastatic breast cancer (second line)	NA[44]	Phase III RCT	Eribulin	Capecitabine	PFS; OS	NA
13-02-2017	Fulvestrant + palbociclib	Metastatic breast cancer (second line)	PALOMA-3 [45]	Phase III RCT	Fulvestrant + palbociclib	Fulvestrant + placebo	PFS	4
13-02-2017	Letrozole + palbociclib	Metastatic hormone receptor-positive breast cancer	PALOMA-2 [46]	Phase III RCT	Palbociclib + letrozole	Letrozole + placebo	PFS	2
03-04-2017	Olaparib	Recurrent platinum-sensitive ovarian cancer	Study 19[22]	Phase II RCT	Olaparib	Placebo	PFS	3
03-04-2017	Olaratumab + doxorubicine	Advanced soft-tissue sarcoma (first line)	NA[47]	Phase II RCT	Olaratumab + doxorubicine	Doxorubicine	PFS	NA
02-05-2017	Afatinib	Advanced squamous cell lung cancer (second line)	LUX-Lung 8 [48]	Phase III RCT	Afatinib	Erlotinib	PFS	2
02-05-2017	Pembrolizumab	Advanced NSCLC (first line)	KEYNOTE-024 [49]	Phase III RCT	Pembrolizumab	Chemotherapy	PFS	5
02-05-2017	Pembrolizumab	Advanced NSCLC (PD-L1 TPS ≥50%; second line)	KEYNOTE-010 [50]	Phase II/III RCT	Pembrolizumab	Docetaxel	PFS; OS	5

(*continued on next page*)

Table 2 (*continued*)

Publication date cieBOM's assessment report	Treatment	Indication	Study name	Study design	Experimental arm (s)	Comparator arm (s)	Primary endpoint (s)	ESMO-MCBS score
05-06-2017	Nanoliposomal irinotecan + fluorouracil + folinic acid	Metastatic pancreatic cancer (second line)	NAPOLI-1[51]	Phase III RCT	Nanoliposomal irinotecan + fluorouracil + folinic acid	Fluorouracil + folinic acid	OS	3
05-06-2017	Lenvatinib + everolimus	Advanced ccRCC (second line)	NA[52]	Phase II RCT	Lenvatinib + everolimus	Lenvatinib or everolimus	PFS	4
10-07-2017	Nivolumab	Recurrent squamous cell carcinoma of the head and neck (second line)	CheckMate 141[27]	Phase III RCT	Nivolumab	Chemotherapy	OS	5
10-07-2017	T-VEC	Advanced melanoma	OPTiM[10]	Phase III RCT	T-VEC	GM-CSF	DRR	NA
02-10-2017	Osimertinib	NSCLC	AURA3[53]	Phase III RCT	Osimertinib	Platinum-pemetrexed	PFS	4
02-10-2017	Ribociclib + letrozole	Metastatic hormone receptor-positive breast cancer (first line)	MONALEESA-2[54]	Phase III RCT	Ribociclib + letrozole	Letrozole + placebo	PFS	4
27-11-2017	Pembrolizumab	Advanced urothelial carcinoma (second line)	KEYNOTE-045 [13]	Phase III RCT	Pembrolizumab	Chemotherapy	PFS; OS	4
27-11-2017	Regorafenib	Hepatocellular carcinoma (second line)	RESORCE[14]	Phase III RCT	Regorafenib	Placebo	OS	4
22-12-2017	^{177}Lu-Dotatate	Midgut neuroendocrine tumors (second line)	NETTER-1[55]	Phase III RCT	^{177}Lu-Dotatate + octreotide LAR	Octreotide LAR	PFS	4
22-12-2017	Bevacizumab + erlotinib	Non-squamous NSCLC (first line)	JO25567[56]	Phase II RCT	Bevacizumab + erlotinib	Erlotinib	PFS	3

Abbreviations: ADT, androgen-deprivation therapy; AEs, adverse events; ccRCC, clear cell renal cell carcinoma; cieBOM, Committee for the Evaluation of Oncological Agents; DRR, durable response rate; ESMO-MCBS, European Society for Medical Oncology - Magnitude of Clinical Benefit Scale; GM-CSF, granulocyte macrophage colony-stimulating factor; NA, not available; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; T-VEC, talimogene laherparepvec; TPS, tumor proportion score.

shown in Table 3; the outcomes of all individual assessments are presented in Table 4. The initial assessment consisted of 33 (80%) positive assessments and 7 (17%) negative assessments. Talimogene laherparepvec for advanced melanoma was considered not assessable because the primary endpoint of the phase III RCT on which the assessment was based, i.e., durable response rate, could not be assessed using the PASKWIL criteria for non-curative SACTs. [10].

Replacing the "*OR*" approach by an "*AND*" approach (scenario 1) resulted in a substantial decrease in the number of positive assessments (from 33 [80%] to 22 [54%]), and, as a consequence, in an increase in the number of negative assessments (from 7 [17%] to 15 [37%]). This predominantly affected immunotherapies such as nivolumab and pembrolizumab. For example, although nivolumab for advanced clear cell renal cell carcinoma (ccRCC) [11] and advanced non-squamous non-small cell lung cancer (NSCLC) [12] and pembrolizumab for advanced urothelial carcinoma [13] demonstrated a clinical benefit in terms of median OS, the point estimates of the HRs were greater than 0.70 (see Supplementary Table 2).

Using an HR threshold of less than 0.60 (scenario 2) resulted in a further increase in the number of negative assessments (from 15 [37%] to 19 [46%]). The outcome of the assessment of regorafenib for hepatocellular carcinoma [14] became negative instead of positive.

Table 3
Summary of the outcomes of the initial assessment and scenarios.

	Positive	Negative	Not assessable
Initial assessment	33 (80%)	7 (17%)	1 (2%)
Scenario 1	22 (54%)	15 (37%)	4 (10%)
Scenario 2	21 (51%)	19 (46%)	1 (2%)
Scenario 3	19 (46%)	18 (44%)	4 (10%)
Scenario 4	21 (51%)	16 (39%)	4 (10%)
Sub-scenario 4a[a]	24 (59%)	14 (34%)	3 (7%)
Sub-scenario 4b[b]	24 (59%)	14 (34%)	3 (7%)

[a] Sub-scenario 4a assessed the impact of accounting for long-term outcomes.
[b] Sub-scenario 4b assessed the impact of accounting for the lower limit of the 95% confidence interval for the hazard ratio.

Furthermore, the outcomes of the assessments of two treatments for advanced melanoma (i.e., dabrafenib plus trametinib [15,16] and pembrolizumab [17]) and docetaxel plus androgen-deprivation therapy (ADT) for metastatic hormone-sensitive prostate cancer [18,19] became negative instead of not assessable.

Changing the threshold for the difference in median survival from more than 12 weeks to more than 16 weeks for RCTs where the median OS in the comparator arm was more than one year (scenario 3) slightly decreased the number of positive assessments (from 22 [54%] to 19 [46%]). The outcome of the assessments of bevacizumab for platinum-resistant ovarian cancer [20], cabozantinib for advanced ccRCC [21], and olaparib for recurrent platinum-sensitive ovarian cancer [22] became negative instead of positive. Both treatments for ovarian cancer, however, did not demonstrate a statistically significant improvement in OS (see Supplementary Table 2).

The inclusion of thresholds for OS rates (scenario 4) slightly mitigated the impact of applying an "*AND*" approach, because it prevented bevacizumab for advanced cervical cancer [23] and nivolumab for advanced non-squamous NSCLC [12] from being assessed negatively. Although the point estimates of the HRs were greater than 0.70, the three-year OS rate for bevacizumab and the two-year OS rate for nivolumab were both higher than 10% (see Supplementary Table 2). Moreover, accounting for long-term outcomes (sub-scenario 4a) and for the lower limit of the 95% CI of the HR (sub-scenario 4b) even further mitigated the impact of applying an "*AND*" approach. Together, these adjustments resulted in positive assessments for five treatments that were otherwise assessed negatively or considered not assessable: pembrolizumab for advanced melanoma [17,24] and advanced urothelial carcinoma [13,25], docetaxel plus ADT for metastatic hormone-sensitive prostate [18,19], and nivolumab for advanced ccRCC [11,26] and recurrent squamous cell carcinoma of the head and neck [27,28]. Four of these treatments were also assessed positively in the initial assessment (see Table 4).

Table 4
Outcomes of all individual assessments.

Treatment	Indication	Initial assessment	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Ramucirumab	Advanced gastric cancer (second line)	Positive	Negative	Negative	Negative	Negative
Cabozantinib	Advanced medullary thyroid cancer	Positive	Positive	Positive	Positive	Positive
Bevacizumab	Platinum-resistant ovarian cancer	Positive	Positive	Positive	Negative	Negative
Bevacizumab	Advanced cervical cancer	Positive	Negative	Negative	Negative	Positive
Lanreotide	Metastatic enteropancreatic neuroendocrine tumors	Positive	Positive	Positive	Positive	Positive
Nivolumab	Advanced melanoma	Positive	Positive	Positive	Positive	Positive
Nivolumab	Advanced squamous cell NSCLC (second line)	Positive	Positive	Positive	Positive	Positive
Dabrafenib + trametinib	Advanced melanoma	Positive	Not assessable	Negative	Not assessable	Not assessable
Pembrolizumab	Advanced melanoma	Positive	Not assessable	Negative	Not assessable	Not assessable[a]
Vemurafenib + cobimetinib	Advanced melanoma	Positive	Positive	Positive	Positive	Positive
Crizotinib	Advanced NSCLC	Positive	Positive	Positive	Positive	Positive
Lenvatinib	Refractory thyroid cancer	Positive	Positive	Positive	Positive	Positive
Necitumumab + gemcitabine + cisplatin	Advanced squamous cell NSCLC	Negative	Negative	Negative	Negative	Negative
Nintedanib + docetaxel	Advanced NSCLC (second line)	Negative	Negative	Negative	Negative	Negative
Docetaxel + ADT	Metastatic hormone-sensitive prostate cancer	Positive	Not assessable	Negative	Not assessable	Not assessable[b]
Nivolumab	Advanced ccRCC (second or third line)	Positive	Negative	Negative	Negative	Negative[b]
Nivolumab	Advanced non-squamous NSCLC	Positive	Negative	Negative	Negative	Positive
Ramucirumab + FOLFIRI	Metastatic colorectal cancer (second line)	Negative	Negative	Negative	Negative	Negative
Nivolumab + ipilimumab	Advanced melanoma	Positive	Positive	Positive	Positive	Positive
Ramucirumab + docetaxel	Advanced NSCLC (second line)	Negative	Negative	Negative	Negative	Negative
TAS-102	Refractory metastatic colorectal cancer	Positive	Negative	Negative	Negative	Negative
Cabozantinib	Advanced ccRCC (second line or higher)	Positive	Positive	Positive	Negative	Negative
Everolimus	Advanced, non-functional neuroendocrine tumors	Positive	Positive	Positive	Positive	Positive
Eribulin	Metastatic breast cancer (second line)	Negative	Negative	Negative	Negative	Negative
Fulvestrant + palbociclib	Metastatic breast cancer (second line)	Positive	Positive	Positive	Positive	Positive
Letrozole + palbociclib	Metastatic hormone receptor-positive breast cancer	Positive	Positive	Positive	Positive	Positive
Olaparib	Recurrent platinum-sensitive ovarian cancer	Positive	Positive	Positive	Negative	Negative
Olaratumab + doxorubicine	Advanced soft-tissue sarcoma (first line)	Positive	Negative	Negative	Negative	Negative
Afatinib	Advanced squamous cell lung cancer (second line)	Negative	Negative	Negative	Negative	Negative
Pembrolizumab	Advanced NSCLC (first line)	Positive	Positive	Positive	Positive	Positive
Pembrolizumab	Advanced NSCLC (PD-L1 TPS $\geq$50%; second line)	Positive	Positive	Positive	Positive	Positive
Nanoliposomal irinotecan + fluorouracil + folinic acid	Metastatic pancreatic cancer (second line)	Positive	Negative	Negative	Negative	Negative
Lenvatinib + everolimus	Advanced ccRCC (second line)	Positive	Positive	Positive	Positive	Positive
Nivolumab	Recurrent squamous cell carcinoma of the head and neck (second line)	Negative	Negative	Negative	Negative	Negative[a]
T-VEC	Advanced melanoma	Not assessable	Not assessable	Not assessable	Not assessable	Not assessable
Osimertinib	NSCLC	Positive	Positive	Positive	Positive	Positive
Ribociclib + letrozole	Metastatic hormone receptor-positive breast cancer (first line)	Positive	Positive	Positive	Positive	Positive
Pembrolizumab	Advanced urothelial carcinoma (second line)	Positive	Negative	Negative	Negative	Negative[c]
Regorafenib	Hepatocellular carcinoma (second line)	Positive	Positive	Negative	Positive	Positive
^{177}Lu-Dotatate	Midgut neuroendocrine tumors (second line)	Positive	Positive	Positive	Positive	Positive
Bevacizumab + erlotinib	Non-squamous NSCLC (first line)	Positive	Positive	Positive	Positive	Positive

Abbreviations: ADT, androgen-deprivation therapy; ccRCC, clear cell renal cell carcinoma; GM-CSF, granulocyte macrophage colony-stimulating factor; NSCLC, non–small cell lung cancer; T-VEC, talimogene laherparepvec.

[a] Positive if long-term outcomes were taken into account.

[b] Positive if the lower limit of the 95% confidence interval for the hazard ratio was taken into account.

[c] Positive if either long-term outcomes or the lower limit of the 95% confidence interval for the hazard ratio were taken into account.

4. Discussion

This study evaluated the impact of different thresholds for PFS and OS on the outcome of the assessment of the clinical benefit of newly registered SACTs in the Netherlands. We showed that replacing the "*OR*" approach by an "*AND*" approach substantially reduced the probability of being assessed positively. This was particularly the case for immunotherapies, since the point estimates of the HRs published in the RCTs were often greater than 0.70 (which was the threshold at the time of the initial assessment). Although the inclusion of thresholds for OS rates slightly mitigated the impact of applying an "*AND*" approach, this highly depended on the duration of follow-up in the RCT publications. In most original RCT publications, on which the assessments are usually based, the follow-up duration was often insufficient for estimating two- or three-year OS rates. As a consequence, some treatments were assessed negatively or considered not assessable, while they should have been assessed positively if the assessment was based on long-term outcomes. For example, the duration of follow-up in the original publication of pembrolizumab for advanced urothelial carcinoma [13] was too short (median duration: 14.1 months) for estimating two-year OS rates, but the publication reporting the long-term survival outcomes [25] showed that the difference in two-year OS rates between pembrolizumab and its comparator (i.e., chemotherapy) was more than 10% (see Supplementary Table 2). This highlights the importance of long-term outcomes as well as the importance of conducting reassessments when such evidence becomes available.

We further demonstrated that, in addition to applying an "*AND*" approach, the use of a more restrictive HR threshold (i.e., <0.60) primarily affected the number of treatments that were considered not assessable. Notably, the outcomes of the assessments of two commonly used treatments for advanced melanoma (i.e., dabrafenib plus trametinib [15,16] and pembrolizumab [17]) became negative, while the outcomes of the assessments of their alternatives (i.e., vemurafenib plus cobimetinib [34] and nivolumab [32], respectively) remained positive. This can most likely be attributed to the choice of comparator. For example, in the RCTs on which the assessments of the anti-PD-1 antibodies were based, pembrolizumab was compared with ipilimumab [17] and nivolumab with dacarbazine [32] (which is less efficacious than ipilimumab [57]). A previous network meta-analysis [57] showed that both anti-PD-1 antibodies, pembrolizumab and nivolumab, and both BRAF plus MEK inhibitors, dabrafenib plus trametinib and vemurafenib plus cobimetinib, were comparable in terms of efficacy when compared with the same comparator (i.e., dacarbazine). For cieBOM, it is crucial that the chosen comparator accurately represents the current standard of care. Moreover, the different outcomes of both BRAF plus MEK inhibitors show a potential limitation of not considering AEs when assessing the clinical benefit of SACTs. Previous studies [58,59] indicated that vemurafenib plus cobimetinib was associated with a worse safety profile than dabrafenib plus trametinib, demonstrating a potentially harmful consequence of using more restrictive HR thresholds without considering AEs for patients with advanced melanoma.

Besides the aforementioned findings, we consider two other findings to be noteworthy. Firstly, the RCTs on which the assessments of both dabrafenib plus trametinib for advanced melanoma [15,16] and docetaxel plus ADT for metastatic hormone-sensitive prostate cancer [18,19] were based resulted in conflicting outcomes in some scenarios. For example, the assessment of dabrafenib plus trametinib for advanced melanoma was based on the following RCTs: Combi-V [15] (with vemurafenib as the comparator) and Combi-D [16] (with dabrafenib as the comparator). In the third and fourth scenarios, the assessment based on Combi-V resulted in a positive outcome, while the assessment based on Combi-D resulted in a negative outcome (see Supplementary Table 2). In our study, these treatments were considered not assessable. However, in practice, cieBOM should provide guidance on the use of such treatments. It is, therefore, important that they determine how treatments should be assessed in case multiple RCTs are available but do not result in similar outcomes. Secondly, the scenario that aligns most closely with the revised PASKWIL criteria (scenario 3) resulted in a negative assessment for four treatments that were assigned an ESMO-MCBS score of 4 or 5. This discrepancy can be predominantly explained by differences in the definition of the HR thresholds (i.e., cieBOM takes into account the point estimate [7], whereas ESMO takes into account the lower limit of the 95% CI [4]) and the use of long-term outcomes. The sub-scenarios within the fourth scenario showed that when both long-term outcomes (sub-scenario 4a) and the lower limit of the 95% CI for the HR (sub-scenario 4b) are taken into account, the outcome of the assessments of three of the four treatments (i.e., nivolumab for advanced ccRCC [11,26] and recurrent squamous cell carcinoma of the head and neck [27,28], and pembrolizumab for advanced urothelial carcinoma [13,25]) will become positive (see Table 4). The outcome of the assessment of the other treatment, i.e., bevacizumab for platinum-resistant ovarian cancer [20], will remain negative as this treatment did not demonstrate a statistically significant improvement in OS. For this treatment, the high ESMO-MCBS score was due to an improvement in QoL [60]. As mentioned earlier, secondary endpoints such as QoL are not taken into account in the assessment of the clinical benefit of SACTs in the Netherlands.

In conclusion, our study showed that applying an "*AND*" approach and using more restrictive thresholds for the HR and difference in median survival had a substantial impact on the outcome of the assessment, resulting in a more than twofold increase in the number of negative assessments. This was not limited to treatments with only marginal survival benefits but also affected those with the highest ESMO-MCBS scores (i.e., 4 or 5). Therefore, it is essential to acknowledge and consider the potential challenges that may arise from applying stricter PASKWIL criteria. This is especially important since the revised criteria include both the "*AND*" approach and the more restrictive threshold for the difference in median survival, without taking into account thresholds for OS rates.

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CRediT authorship contribution statement

Nicolas S.H. Xander: Writing – review & editing, Methodology, Conceptualization. **W. Edward Fiets:** Writing – review & editing, Methodology, Conceptualization. **Brenda Leeneman:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Formal analysis, Conceptualization. **Carin A. Uyl-de Groot:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **A.N. Machteld Wymenga:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **An K.L. Reyners:** Writing – review & editing, Methodology, Conceptualization. **Wouter K. de Jong:** Writing – review & editing, Methodology, Conceptualization. **Nathalie E.M. Uyl:** Writing – review & editing, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114002.

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